5

The Scientific Basis for PREP Assessment

Assessing health risks from conventional tobacco products is similar to that for many environmental and occupational exposures. Tobacco risks, however, are among the more complicated to assess for several reasons. The general components of risk assessment (hazard identification, dose-response assessment, exposure assessment, and risk characterization) described in Chapter 1 are still useful to consider (see Table 5-1).

Hazard identification is challenging because tobacco and the smoke generated upon its combustion are complex mixtures. Some of the hundreds (or thousands) of known or suspected toxicants are fairly well understood; however, the relative contribution to overall toxicity of most of the individual compounds is not. In addition, tobacco products contain added constituents or ingredients, but the identity and concentration of these compounds within a specific tobacco product is unknown, due to proprietary concerns. Animal models of tobacco toxicity are limited, posing additional barriers to complete hazard identification.

Dose-response assessment is complicated. Because the exposure is a complex mixture, the diseases associated with tobacco exposure are many and the dose-response relationships vary significantly. Assessing the dose in epidemiological studies is complicated in part by the factors described for hazard identification. In addition, the dose a tobacco user is exposed to can change often over a long and variable smoking history. Finally, the responses are most often diseases with long periods of disease progression until diagnosis and from time point of dose estimation.

Exposure assessment is difficult for some of the same reasons. There is a multiplicity of tobacco products on the market. The specific exposures associated with any one 'branded' product could change throughout time because the product can change. Changes in exposure throughout time are not documented. In addition, smokers of "low-yield" products often compensate (change smoking behavior to increase nicotine exposure), so their exposures to nicotine and tobacco/smoke toxicants are often higher than predicted by a common form of exposure assessment, self-report.

The objective of a potential reduced-exposure product (PREP) risk assessment is to determine if the risk of harm from the use of the PREP is less than the risk of harm in the absence of the PREP (see Table 5-1). The risk management objective considered by the committee is not to ban or control the exposure per se, as is the case for environmental and occupational exposures. The risk management objective, as will be made clear in Chapter 7, is primarily to verify whether or not a product is associated with either exposure reduction or harm reduction.

A PREP risk assessment involves lowering the dose of a complex mixture in a person (or population) with varying degrees of pre-existing pathology or cellular damage caused by a complex mixture exposure (that of conventional products) and trying to reverse early damage or to stop disease progression. This is problematic at this point, as there are no adequate human or animal studies that replicate this scenario. While some studies report risks in persons who switch from nonfiltered cigarettes to filtered cigarettes, or from high- to low-tar cigarettes, this 'switch-

ing' did not reduce exposure (due to compensation) significantly in many people. The reduction in risk, if any, would occur only in persons who do not compensate for lower nicotine levels by smoking more or smoking differently. The basic elements of risk assessment can, however, be still considered. The questions become slightly different, and the data required or the study designs might be different from that required for a tobacco risk assessment.

For *hazard identification*, the questions include:

- Does the PREP contain (or produce during use) toxicants known to cause adverse health effects?
- To what extent are the compounds targeted for reduced exposure causally linked to a tobacco-related disease?
- How does its content compare with the toxicants in the conventional tobacco product to which it is compared?
- Are there unique toxicants in a PREP compared to conventional tobacco products?

For hazard identification, it is essential to know the composition of the material to which people will be exposed from the PREP compared to the standard product. Any new material, such as flavors, added to standard products must be included in the analyses. It is important to analyze the product that actually enters the body (for example, the combustion products that are inhaled) rather than the composition of the product as sold.

The approach to testing the toxicity of the material to which people are exposed in the tobacco-related PREP compared to standard tobacco products is discussed in Chapter 10. The objectives of the toxicity tests are to determine what toxic effects can be induced by the test materials (the tobacco-related PREP compared to the standard product) and how much of the test materials is required to cause the adverse effect, i.e., the dose–response characteristics in animals of the test materials. Data from animal studies can be used to eliminate new products that are much more toxic than existing ones.

A series of comparative potency tests is appropriate. In vitro studies in cultured cells from both animals and humans can be used to determine the ability of the test materials (from the tobacco-related PREP and the standard product) to induce cellular damage, an inflammatory response, or cell death. Assays of the mutagenic or clastogenic activity of the test materials can be done in bacterial or mammalian cell systems.

In animal studies, tests for tobacco-related toxicity should include evaluation of the ability to induce adverse health effects or cancer in the respiratory tract, the nervous system, the cardiovascular system, the reproductive and developmental systems and other organs. Toxicokinetic studies should be used to determine dosimetry to different organs and to suggest biomarkers of internal dose that can be used in humans. Short-term clinical tests in humans should be done to compare the potencies of the test materials to induce acute adverse health effects (such as reduced pulmonary function) and to determine the toxicokinetics of the tobacco-related PREP compared to the standard product.

For *dose-response assessment*, the questions include:

- What are the dose/response characteristics of the PREP compared to the conventional tobacco product?
- Do smokers use PREPs at a time in their individual smoking history (and there-